(19) Patent Office of Japan (JP)(11) Publication of Patent Application

JAPANESE PATENT APPLICATION (KOKAI)(A) 9-59218

(43) Publication: Hei-Sei 9 (1997) 3/4

Int. CL. 5	ID Code	Office Cont'l No.	F1
C 07 C 69/68			
C 07 F 7/18			A
C 08 G 63/06			NLP
A 01 N 37/36			

Verification request: Not requested

Number of claims of the invention: 1 OL

Number of pages (total of 12 pages)

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(21) Filed Number: Application Hei-Sei 7-217345

(22) Filed Date: Hei-Sei 7 (1995) 8/25

(71) Patent Assignee: Shimatsu Manufacturing Company

JP 9-59218

[Note: Names, addresses, company names and brand names are translated in the most common manner. Japanese language does not have singular or plural words unless otherwise specified by a numeral prefix or a general form of plurality suffix.]

(54) [Name of the Invention]

(57) [Summary]

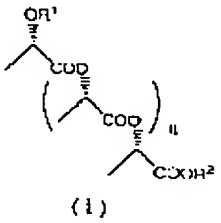
[Problem]

The problem according to the present invention is to suggest a novel L-lactic acid oligomer derivative material that can be obtained as a pure compound.

[Solution Measures]

The L-lactic acid oligomer derivative material is represented according to the shown below general formula (I).

[Formula 1]



(I)

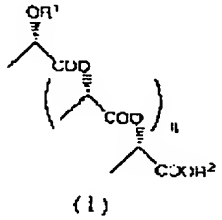
Here, R1 represents H, alkyl radical, aryl radical, acyl radical or silyl radical, R2 represents H, alkyl, radical or aryl radical, however, where R1 and R2 cannot become both simultaneously H, and where n is an integer number in the range of 0 ~ 20.

[Scope of the Patent Claims]

[Claim 1]

L-lactic acid oligomer derivative material represented according to the shown below general formula (I):

[Formula 1]



(I)

Here, R1 represents H, alkyl radical, aryl radical, acyl radical or silyl radical, R2 represents H, alkyl, radical or aryl radical, however, where R1 and R2 cannot become both simultaneously H, and where n is an integer number in the range of 0 ~ 20.

[Detailed Explanation of the Invention]

[0001]

[Technical Field Pertinent to the Present Invention]

The present invention is an invention about a novel L-lactic acid oligomer derivative material.

[0002]

[Previous Technology]

Practical experiments have been conducted regarding results for the lactic acid growth promoting effect relative to plants, beginning with the report using ginseng (or carrots) published in 1924 (Blumenthal F and Meyer P (1924) Uber durch Acidum Lacticum erzeugte Tumoren auf Mohrrubenscheiben. Z. f. Kregsg. 21: 250 – 252.) Also, practical experiments have been conducted using other plants, namely, marigolds, sunflowers, sugarcane, and the growth promoting effect of the lactic acid has been confirmed (Hildebrandt AC, Rikker Ajand Watertor JI (1954) Growth and Inhibition of tissue cultures on media with different concentrations of organic acids. Phytopathology 44: 422 – 428.)Then, active research has been conducted on the active properties possessing substance where in an aqueous lactic acid solution lactic acid oligomer is mixed and made present, and it has been made clear that the main substance of the plant growth promoting effect materials is not the lactic acid monomer, but it is the L-lactic acid oligomer (Alan M. Kinnersley, Taylor C. Scott III, John H. Yopp and Gerge H. Whitten (1990) Promotion of plant growth by polymers of lactic acid. Plant Growth Regulation 9: 137 – 146.)

[0003]

Thus the L-lactic acid oligomer is an effective material that has a plant growth promoting effect.

[0004]

Regarding the previous technology for the preparation of lactic acid oligomer material, it is said that the mixed oligomer material obtained as lactic acid is heated is separated and purified by using column chromatography, and divided fractions at different polymerization levels are obtained. However, it is difficult to obtain a pure form oligomer by the method using separation of the oligomer mixed material by gel filtration column. Especially, extremely high (purity) substance has not been obtained. Consequently, in the case when farm products activation by using oligomers obtained by the separation purification method according to the previous technology has been studied, the oligomer purity has generally been insufficient. Also, if it is not a pure oligomer, it is difficult to freely conduct its chemical modification.

[0005]

[Problems Solved by the Present Invention]

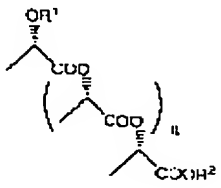
Here, the goal of the present invention is to suggest a novel L-lactic acid oligomer derivative material that can be obtained as a pure compound.

[0006]

[Measures in Order to Solve the Problems]

The L-lactic acid oligomer derivative material according to the present invention is a material that can be represented according to the general formula (i) shown here below:

[Formula 2]



(1)

Here, R1 represents H, alkyl radical, aryl radical, acyl radical or silyl radical, R2 represents H, alkyl, radical or aryl radical, however, where R1 and R2 cannot become both simultaneously H, and where n is an integer number in the range of 0 ~ 20.

[0007]

Here below, the present invention will be explained in further details.

[0008]

As the alkyl radical denoted by the R1 that is found in the general formula (I), for example, methyl thio methyl (MTM), benzyl oxy methyl (BOM), p-methoxy benzyl oxy methyl (PMBM), (4-methoxy phenoxy) methyl (p-AOM), (4-methoxy phenyl) methyl, t – butyl dimethyl siloxy methyl, t – butyl diphenyl siloxy methyl, 2, 2, 2 – trichloro ethoxy methyl, 2, 2, 2 – trichloroethyl, tetrahydro furanyl, allyl, 1-ethoxy methyl, 1 – ethoxy ethyl, benzyl, substituted benzyl, 2 – (trimethyl silyl) ethoxy methyl (SEM), etc., derived radicals can be listed. Among these, t-butyl dimethyl siloxy methyl, t – butyl dimethyl siloxy methyl, t-butyl diphenyl siloxy methyl, 2 – (trimethyl silyl) ethoxy methyl radical, are preferred from the point of view that they can be incorporated and their protection can be removed at more moderate temperatures.

[0009]

As the aryl radicals used as R1, for example, it is possible to list substituted or un-substituted phenyl radicals, and as the substitution radicals in this case, for example, p-methoxy radicals etc., can be used.

[0010]

As the R1 acyl radicals, for example, it is possible to list the following: monochloro acetyl, dichloro acethyl, methoxy acetyl, phenoxy acetyl, reurinoyl, methoxy carbonyl, 2, 2, 2 – trichloro ethoxy carbonyl, 2 – (trimethyl silyl) ethoxy carbonyl, allyl oxy carbonyl, etc., protected radicals. Among these, monochloro acetyl, reurinoyl radical, are preferred because of the fact that that they can be incorporated and their protection can be removed at more moderate temperatures.

[0011]

As the silyl radicals used as the R1 radicals, for example, t-butyl dimethyl silyl (TBDMS), t-butyl diphenyl silyl (TBDPS), triisopropyl silyl (TIPS), timethyl tekcyl silyl (TDS), triphenyl silyl (TPS), etc., protected radicals can be used. Among these, t-butyl dimethyl silyl , t – butyl diphenyl silyl radicals are preferred from the point of view that the handling of the raw materials is easy and the incorporation and the removal of the protection are easy.

[0012]

As the alkyl radicals used as the R2 in the general formula (I), for example, methyl thio methyl, 2 – (trimethyl silyl) ethoxy methyl, benzyl oxy methyl, phenacyl, p-bromo phenacyl, N-phthaloimide methyl, 2, 2, 2 – trichloro ethyl, allyl, benzyl, substituted benzyl, etc., protected radicals can be listed. Among these, phenacyl, p-bromo phenacyl,

2, 2, 2 – trichloro ethyl, benzyl, substituted benzyl radical are preferred from the point of view that the introduction and the removal of the protection can be conducted at milder temperatures.

[0013]

As the aryl radicals used, for example the protected radicals of substituted or non-substituted phenyl radicals can be used.

[0014]

According to the present invention, R1 and R2 cannot become both simultaneously H, however, if at least one of the R1 or R2 is not H, then they can be the same or different and these are both good options.

[0015]

Regarding preferred combinations among these R1 and R2, there are the materials where R1 is any one of t-butyl dimethyl siloxy methyl, t-butyl diphenyl siloxy methyl, 2 – (trimethyl silyl) ethoxy methyl, 2 – (trimethyl silyl) ethoxy carbonyl, t-butyl dimethyl silyl, t-butyl diphenyl silyl, triisopropyl silyl, dimethyl texyl silyl, triphenyl silyl radicals, and R2 is any one of the phenacyl, p-bromo phenacyl, N – phthaloimide methyl, 2, 2, 2 – trichloro ethyl radical, and the materials where R1 is any one of the methyl thio methyl, benzyl oxy methyl, p-methoxy benzyl oxy methyl, (4-methoxy phenyl) methyl, 2, 2, 2 – trichloro ethoxy methyl, 1-ethoxy ethyl, benzyl, substituted benzyl, 2, 2, 2 – trichloro ethyl, mono chloro acetyl, dichloro acetyl, reurinoyl, 2, 2, 2 – trichloro ethoxy carbonyl, alklyl oxy carbonyl radical, and R2 is 2- (trimethyl silyl) ethoxy methyl, etc.

[0016]

After that an explanation will be provided regarding the method of synthesis of a lactic acid oligomer with the general formula (I). Generally, the L-lactic acid oligomer according to the present invention can be obtained as L-lactic acid monomer material where the carboxyl radical is protected by the R2 radical, or the hydroxyl radical of the oligomer, and the L-lactic acid monomer material where the hydroxyl radical is protected by the R1 radical or the carboxylic acid or acid halide derivatives of the oligomer, are condensed; and the materials where R1 or R2 are H, are obtained as the carboxylic radical or the hydroxyl radical are stripped of their protection.

[0017]

Namely, the synthesis scheme is illustrated here below and an explanation is provided regarding the synthesis method of the lactic acid oligomer according to the general formula (I). Moreover, in the case of this scheme, it is only one example of the synthesis method and it is by no means limiting the scope of the present invention.

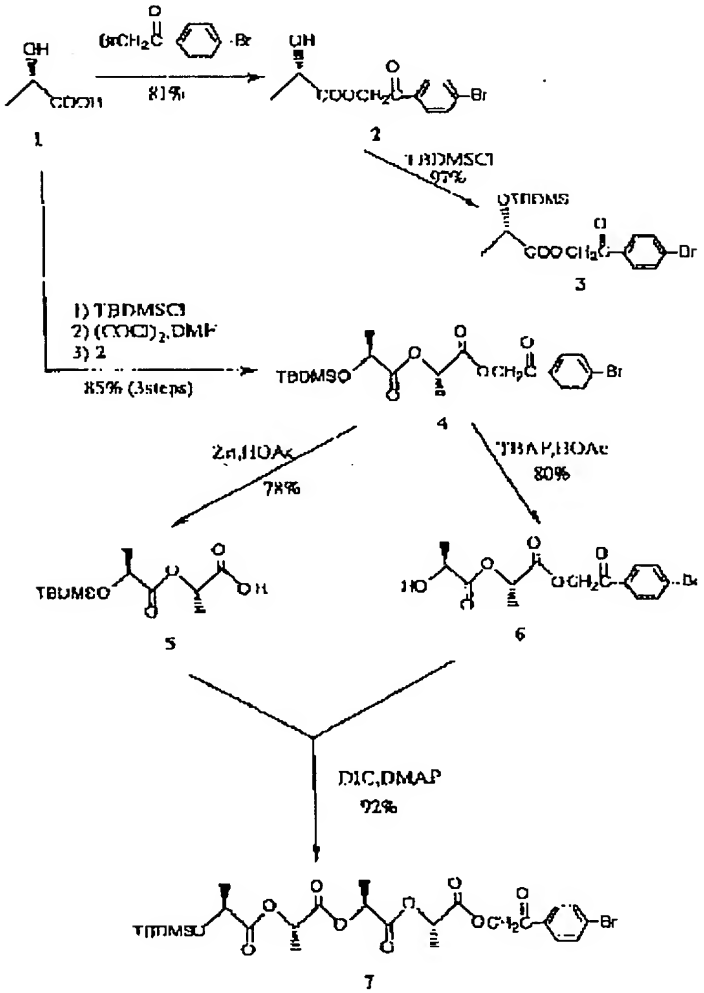
[0018]

Regarding the abbreviation terms used in the scheme, they represent the described here below test chemicals:

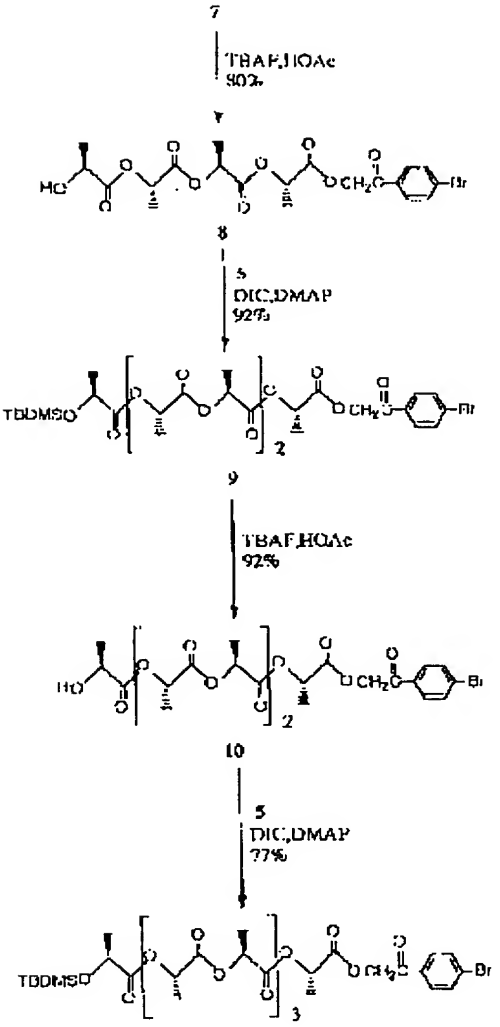
TBDMSC1 = t-butyl dimethyl silyl chloride
DMF = N, N – dimethyl formamide
DIC = diisopropyl carbo diimide
DMAP = 4-dimethyl amino pyridine
TBAF = tetra- n – butyl ammonium fluoride
HOAc = acetic acid

[0019]

[Formula 3]



[Formula 4]



[0020]

First, L-lactic acid (1) is reacted with p-bromo phenacyl bromide, and the carboxyl radical protected compound (2) is obtained. After that, the hydroxyl radical of the compound (2) is protected by using t-butyl dimethyl silyl chloride and the compound (3) is obtained.

[0021]

On the other hand, from the L-lactic acid (1), by using three technological processes, namely, both the hydroxyl radical and the carboxyl radicals are protected (hindered) by using t-butyl dimethyl silyl chloride, and after that, the material is treated using

chlorinated oxalyl, DMF, and the derivative material that is an acid chloride of the L-lactic acid where the hydroxyl radical is protected, is obtained, and this acid chloride is reacted with the compound (2), and the L-lactic acid dimer material (4), is obtained.

[0022]

After that, the p-bromo phenacyl radical of the dimer material is treated in acetic acid by using zinc, and it is converted into the carboxylic acid (5). Also, on the other hand, the t-butyl dimethyl silyl radical of the dimer material (4), in acetic acid, and by using tetra – n – butyl ammonium fluoride, is guided towards the alcohol (6). The obtained this way two compounds, namely, the dimer material carboxylic acid (5), and the dimer material alcohol (6) are condensed by using diisopropyl carbo diimide, and the L-lactic acid tetramers material (7), is obtained.

[0023]

The t-butyl dimethyl silyl radical of this tetramers material (7), in acetic acid, and by using tetra – n – butyl ammonium fluoride, is stripped of the protection and it is directed towards the tetramers material alcohol (8), and it is condensed with the dimer material carboxylic acid (5) and L-lactic acid hexamer material ((, with incorporated (diisopropyl carbodiimde/methylene chloride), is obtained.

[0024]

By using the same procedure, the obtained hexamer material (9) is guided to the alcohol (10) (tetra – n – butyl ammonium fluoride), and it is condensed with the dimer material carboxylic acid (5) (diisopropyl carbodiimide/methylene chloride), and the L-lactic acid octamer material (11), is obtained.

[0025]

Also, the alcohol (20 with protected carboxyl radicals and the dimer material carboxylic acid (5) where the hydroxyl radicals are protected, are condensed, (diisopropyl carbodiimide/methylene chloride), and L – lactic acid trimer material is obtained.

[0026]

Also, the p-bromo phenacyl radical of the tetramers material (7), in acetic acid, is treated by using zinc, and it is converted into tetramer material carboxylic acid where the hydroxyl radical is protected, and this tetramer material carboxylic acid and the alcohol (2) are condensed (diisopropyl carbodiimide/methylene chloride), and L-lactic acid pentamer material is obtained.

[0027]

The same way, the p-bromo phenacyl radical of the tetramers material (7), in acetic acid, is treated by using zinc, and it is converted into hexamer material carboxylic acid where the hydroxyl radical is protected, and this hexamer material carboxylic acid and the alcohol (2) are condensed (diisopropyl carbodiimide/methylene chloride), and L-lactic acid heptamer material is obtained.

[0028]

By following these procedures it is possible to obtain the 2 ~ 8 mer materials of the L-lactic acid (n = 0 ~ 6) as pure compounds. Here below, by repeating the same reactions it is possible to obtain the 9 ~ 22 mer materials of the L-lactic acid (n = 7 ~ 20) as pure compounds.

[0029]

According to this synthesis method, for the incorporation of the R1 radical, which is used as the protection (hindering) radical of the hydroxyl radical, usually, R1 X (where, R1 represents an alkyl radical, aryl radical, acyl radical, or a silyl radical, and X represents halogen (Cl, Br, I)), can be used.

[0030]

Also, regarding the R1 radical protection removal, it can be appropriately conducted under protection removal conditions that correspond to the type of the R1 of the L-lactic acid derivative material, namely, it can be conducted by using tetra – n – butyl ammonium chloride, thio urea, hydrazine acetic acid salt, zinc acetate, contact hydrogenation, chlorinated silver hydride etc., and conducting the treatment under conditions where there is no effect on the other functional radicals.

[0031]

On the other hand, for the incorporation of the R2 radical that serves as the protection radical of the carboxylic radical, usually, R2X (where R2 represents an alkyl radical or an aryl radical, and X represents halogen (Cl, Br, I)) can be used.

[0032]

Also, regarding the R2 radical protection removal it can be conducted under appropriate protection removal conditions corresponding to the type of the R2 of the L-lactic acid derivative, and namely, it can be conducted by a treatment under conditions where zinc acetate, tetra – n – butyl ammonium fluoride etc., are used and there is no effect on the other functional radicals.

[0033]

Also, regarding the condensation agent that is used in the condensation between the hydroxyl radical of the L-lactic monomer or oligomer where the carboxylic radical is protected by the R2 radical, and the carboxylic acid of the L-lactic acid monomer or oligomer where the hydroxyl radical is protected by the R1 radical, there are no particular limitations, however, usually, it is possible to use diisopropyl carbodiimide, dicyclohexyl carbodiimide etc., carbodiimide type condensation agents. Also, in this case, it is also proffered to use 4-dimethyl amino pirydine, etc., as catalyst.

[0034]

Also, regarding the condensation agent that is used in the condensation between the hydroxyl radical of the L-lactic monomer or oligomer where the carboxylic radical is protected by the R2 radical, and the acid halide derivative the L-lactic acid monomer or oligomer where the hydroxyl radical is protected by the R1 radical, there are no particular limitations, however, usually, it is possible to use triethyl amine, pyridine etc., de-acidification agents.

[0035]

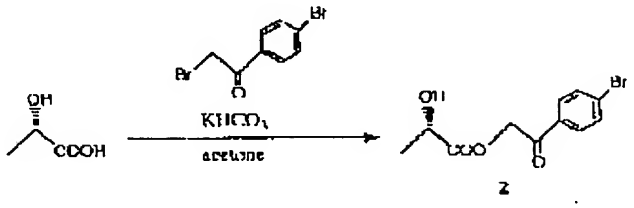
[Practical Examples]

Here below, the present invention will be explained in details by using practical examples, however, the scope of the present invention is by no means limited by the below described practical examples.

[0036]

(Synthesis Example 1)

[Formula 5]



In a 2000 ml capacity flask, 9.73 grams (108.0 mmol) L-lactic acid, 10.81 grams of potassium hydrocarbonate (108.0 mmol) and 30.02 grams of p-bromo phenacyl bromide (108.0 mml) are introduced, and 1600 ml of dried acetone are added, and under nitrogen gas, at room temperature, the material was stirred for a period of 24 hours. The reaction solution was concentrated under reduced pressure, and it was suspended in ethyl acetate, and it was washed using water and saturated table salt water solution. The organic layer was dried by using anhydrous sodium sulfate, it was concentrated under reduced pressure and a crude synthesized material was obtained. The obtained crude synthesized material

was again re-crystallized by using ethyl acetate – hexane and 25.24 grams (yield 81 %) of the target material (2) were obtained.

(2)

Rf = 0.49 (ethyl acetate: hexane = 1: 1)

Mp: 103 – 104oC

$[\alpha]^{20}{}_{D}$ – 0.95° (C=1. 2, CH3OH)

MS (CI, isobutane) 289 [M (^{81}Br) + 1]$^{+}$

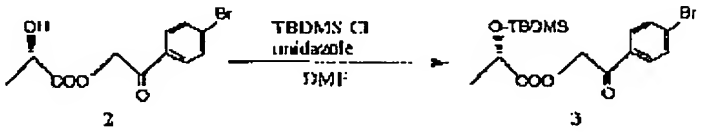
287 [M (^{79}Br) + 1]$^{+}$

^{1}H – NMR (270 MHz, CDCl3)δ: 7.630 ~ 7.800 (4H, m, aromatic protons: AA', BB'), 5.579 (1H, d, 16.8 Hz, AB type A part), 5.340 (1H, d, 16, 8Hz, AB type B part), 5.340 (1H, d, 16.8 Hz, AB type B part), 4,500 (1H, q, 7.0 Hz), 2.799 (1H, br.s, OH), 1.564 (3H, d, 7.0 Hz)

[0037]

(Synthesis Example 2)

[Formula 6]



In a 50 ml capacity flask, to 970 grams (3.38 mmol) of the compound (2) obtained according to the above Synthesis Example 1, under room temperature, 612 mg of t-butyl dimethyl silyl chloride (4.06 mmol), 508 mg of imidazole (7.46 mmol) are added, and this was dissolved in 1.3 ml of dried DMF, and under nitrogen gas, at room temperature, the material was stirred for a period of 24 hours. This mixed material was suspended in hexane and it was washed using water and saturated table salt water solution. The organic layer was dried by using anhydrous sodium sulfate and it was concentrated under reduced pressure. The obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 75 g., ethyl acetate: hexane = 1:9), and 1.32 grams (yield 97 %) of the target material (3), were obtained.

(3)

Rf = 0.52 (ethyl acetate: hexane = 3:17)

Mp: 39 – 41oC

$[\alpha]^{20}{}_{D}$ – 15.1° (C=0.70, CH3OH)

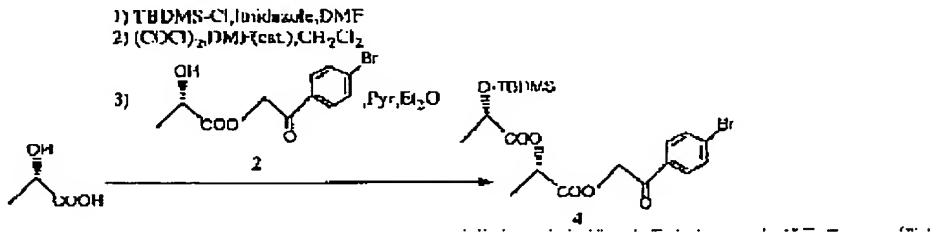
MS (CI, isobutane) 403 $[M\ (^{79}Br) + 1]^{+}$

^{1}H – NMR (270 MHz, CDCl3)δ: 7.606 ~ 7.793 (4H, m, aromatic protons: AA', BB'), 5.360 (1H, d, 16.2 Hz, AB type A part), 5.286 (1H, d, 16, 2Hz, AB type B part), 4.518 (1H, q, 7.0 Hz, AB type B part), 1.515 (3H, d, 7.0 Hz), 0.907 (9H, s, TBDMS), 0.128 (3H, s, TBDMS), 0.120 (3H, s, TBDMS)

[0038]

(Synthesis Example 3)

[Formula 7]



In a 200 ml flask, 5.43 grams of L-lactic acid (60.28 mmol), 21.81 grams of t-butyl dimethyl silyl chloride (144.70 mol), 18.11 grams of imidazole (266.01 mml), were introduced, and this was dissolved in 20 ml of dried DMF. This material was stirred for a period of 18 hours under nitrogen gas and at room temperature. This mixed material was placed in an aqueous solution of saturated sodium hydro carbonate, and it was extracted by using hexane. The organic layer was washed by using saturated table salt aqueous solution, and it was dried by using anhydrous sodium sulfate, and it was concentrated under reduced pressure, and disilylated crude synthesized material was obtained. The obtained crude synthesized material was dissolve din 60 ml of methylene chloride, and the system was acclimated to 0oC and after that 10.72 grams of oxalyl chloride (84.46 mmol) were added, and then, after that 6 drops of DMF were dripped in. At a temperature of 0oC it was stirred for a period of 1 hour and after that at room temperature it was stirred for a period of 2 hours, and it was concentrated under reduced pressure, and the acid chloride crude synthesis material, was obtained. The obtained crude synthesized material was dissolved in 87 ml of diethyl ether, and the system was acclimated to 0oC and after that 34 ml of pyridine and 16.45 grams of the obtained compound (2) according to the above Synthesis Example 1 (57.30 mmol), were sequentially added. At a temperature of 0oC, the material was stirred for a period of 1 hour and after that it was placed in saturated aqueous solution of sodium hydrocarbonate, and it was extracted using ethyl acetate. The organic layer was washed by using 10 % citric acid aqueous solution, and it was washed by using saturated table salt aqueous solution. After that, the

organic layer was dried by using anhydrous sodium sulfate, and it was concentrated under reduced pressure. The obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 600 g., ethyl acetate: hexane = 1:9), and 24.35 grams (yield 85 %) of the target material (4), were obtained.

(4)

Rf = 0.42 (ethyl acetate: hexane = 3:17)

$[\alpha]^{20}{}_{D} - 51.9^{o}$ (C=1.3, CH3OH)

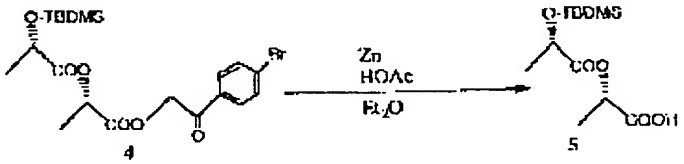
MS (CI, isobutane) 475 $[M (^{79}Br) + 1]^{+}$

^{1}H – NMR (270 MHz, CDCl3)δ: 7.608 ~ 7.778 (4H, m, aromatic protons: AA', BB'), 5.449 (1H, d, 15.9 Hz, AB type A part), 5.245 (1H, q, 7,.2Hz) 5.221 (1H, d, 15.9 Hz, AB type B part), 4.416 (1H, q, 6.5 Hz), 1.664 (3H, d, 7.2 Hz), 1.453 (3H, d, 6.5 Hz), 0.919 (9H, s, TBDMS), 0.117 (3H, s, TBDMS), 0.090 (3H, s, TBDMS)

[0039]

(Synthesis Example 4)

[Formula 8]



In a 1000 ml flask, 5.43 grams (11.47 mmol) of the obtained according to the Synthesis Example 3 compound (4), were dissolved in 370 ml of diethyl ether, and under room temperature, 19.70 ml (344.13 mmol) of acetic acid, were added. To this, under stirring, 22.49 grams (344.04 mmol) of zinc power were added, and at room temperature, it was stirred for a period of 2 hours. This mixed material was filtered by using a glass filter, and the residual material was washed by using ethyl acetate, and a filtered solution was obtained. The filtered solution was extracted by using saturated sodium hydrocarbonate aqueous solution, and citric acid was added to the aqueous layer and the pH was adjusted to be within the range of 4 ~ 5, and it was extracted by using ethyl acetate. Again, the organic layer was extracted by using saturated aqueous solution of sodium hydrocarbon, and citric acid was added and the pH was adjusted within the range of 4 ~ 5, and it was extracted by using ethyl acetate. The organic layer was washed by using saturated table salt water solution, and it was dried by using anhydrous sodium sulfate. The material was concentrated under reduced pressure and 2.47 grams (yield of 78 %) of the target material (5), were obtained.

(5)

Rf = 0.26 (ethyl acetate: hexane = 3:7)

$[\alpha]^{20}{}_{D}$ – 45.6° (C=0.67, CH3OH)

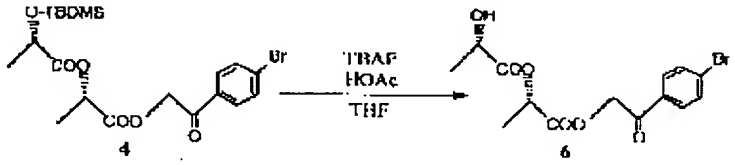
MS (FAB+, m-NBA) 277 $[M + 1)^{+}$, 299 $(M + Na)^{+}$

^{1}H – NMR (270 MHz, CDCl3) δ: 8.670 (1H, br. s. COOH), 5.131 (1H, q, 7.0 Hz), 4.403 (1H, q, 7,.0Hz), 1.546 (3H, d, 7.0 Hz), 1.449 (3H, d, 7.0 Hz), 0.907 (9H, s,TBDMS), 0.111 (3H, s, TBDMS), 0.087 (3H, s, TBDMS)

[0040]

(Synthesis Example 5)

[Formula 9]



Inside a 100 ml flask, 3.50 grams (7.39 mmol) of the compound (4) obtained according to the above Synthesis Example 3, were dissolved in 14.8 ml of tetra hydro furan, under room temperature, 5.08 ml (88.74 mmol) of acetic acid, 14.80 ml (1480 mmol) of a 1 Mole concentration solution of tetra- n- butyl ammonium fluoride in tetrahydro furan, were sequentially added. This material was stirred at room temperature for a period of 24 hours, and it was then diluted by using ethyl acetate, and it was washed using saturated sodium hydro carbonate aqueous solution and saturated table salt aqueous solution. The organic layer was dried by using anhydrous sodium sulfate, and it was concentrated under reduced pressure and the obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 80 g., ethyl acetate: hexane = 2:8), and 2.13 grams (yield 80 %) of the target material (6), were obtained.

(6)

Rf = 0.49 (ethyl acetate: hexane = 1:1)

mp: 70 ~ 72oC

$[\alpha]^{20}{}_{D}$ – 51.2° (C=0.71, CH3OH)

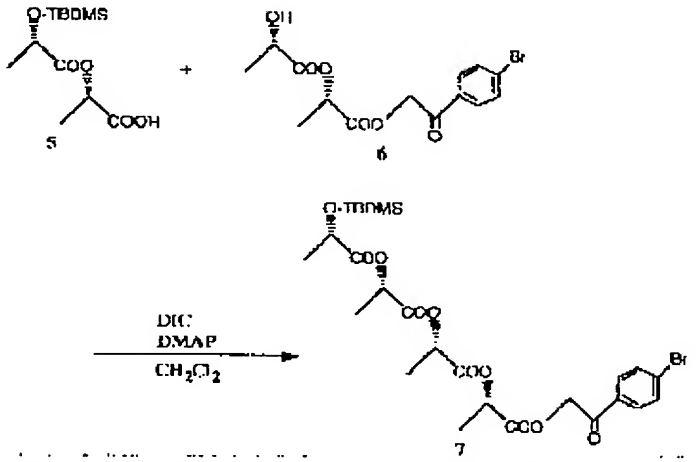
MS (FAB+, m-NBA) 359 $[M (^{79}Br) + 1]^{+}$

^{1}H – NMR (270 MHz, CDCl3) δ: 7.618 ~ 7.789 (4H, m, aromatic protons: AA', BB'), 5.463 (1H, d, 16.4 Hz, AB type A part), 5.336 (1H, q, 6, 8Hz), 5.256 (1H, d, 16.4 Hz, AB type B part), 4,382 (1H, q, 7.0 Hz), 1.692 (3H, d, 6.8 Hz), 1.494 (3H, d, 7.0 Hz)

[0041]

(Synthesis Example 6)

[Formula 10]



In a 100 ml flask, 1.61 grams (5.82 mmol) of the compound (5) obtained according to the Synthesis Example 4 were dissolved in 5.8 ml of methylene chloride, and the system was cooled to 0oC. To that, 500 mg (3.96 mmol) of diisopropyl carbo diimide were added, and at a temperature of 0oC the material was stirred for a period of 10 minutes. Under a temperature of 0oC, 952 grams (2.65 mmol) of the compound (6) obtained according to the Synthesis Example 5 were added and dissolved in 5.8 ml methylene chloride, and then after that 227 mg (1.86 mmol) of 4-dimethyl amino pyridine, were added. This was stirred for a period of 30 minutes at 0oC and after that it was concentrated under reduced pressure. This mixed material was suspended in ethyl acetate, and it was washed by using 10 % citric acid aqueous solution, saturated sodium hydro carbonate aqueous solution, and saturated table salt aqueous solution. The organic layer was dried by using anhydrous sodium sulfate and it was concentrated under reduced pressure. This mixed material was suspended in hexane, filtered, and the filtered solution where the sediment has been removed was obtained. The filtered solution was concentrated under reduced pressure and the obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 130 g., ethyl acetate: hexane = 2:8), and 1.5 grams (yield 92 % from compound (6)) of the target material (7), were obtained.

(7)

Rf = 0.21 (ethyl acetate: hexane = 3:17)
Rf = 0.50 (ethyl acetate: hexane = 1:3)

$[\alpha]^{20}{}_{D}$ – 87.5° (C=1.3, CH3OH)

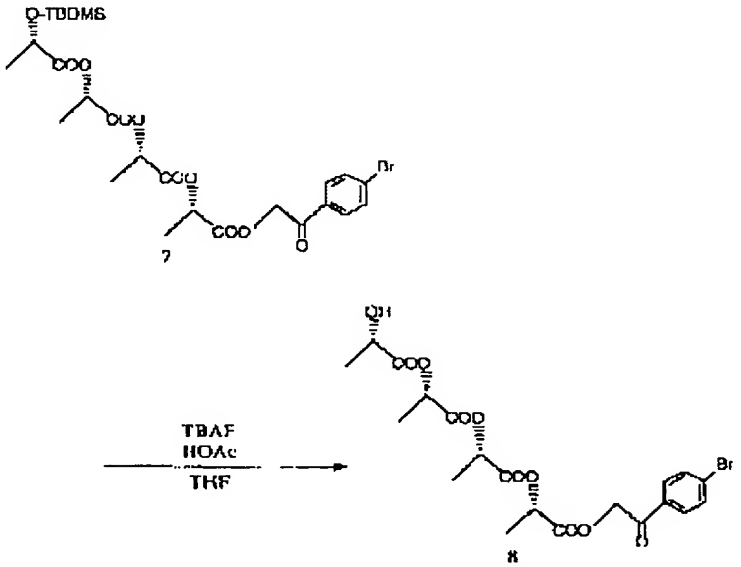
MS (FAB+, m-NBA) 617 [M (^{79}Br) + 1]$^{+}$ 561 (M- tBu)

^{1}H – NMR (270 MHz, CDCl3) δ: 7.625 ~ 7.768 (4H, m, aromatic protons: AA', BB'), 5.456 (1H, d, 16.4 Hz, AB type A part), 5.286 (1H, q, 7.3 Hz), 5.222 (1H, d, 16.4 Hz, AB type B part), 5.200 (1H, q, 7.3 Hz), 5.140 (1H, q, 7.3 Hz), 4.397 (1H, q, 6.5 Hz), 1.669 (3H, d, 7.3 Hz), 1.583 (6H, d, 7.3 Hz), 1.446 (3H, d, 6.5 Hz), 0.902 (9H, s, TBDMS), 0.108 (3H, s, TBDMS), 0.084 (3H, s TBDMS)

[0042]

(Synthesis Example 7)

[Formula 11]



In a 100 ml flask, 1.71 grams (2.77 mmol) of the compound (7) obtained according to the Synthesis Example 6, were dissolved in 5.5 ml of tetrahydro furan at room temperature, and 1.90 ml (33.19 mmol) of acetic acid, 5.54 ml (5.54 mmol) of 1M concentration solution of tetra – n – butyl ammonium fluoride in tetrahydro furan, were sequentially added. The material was stirred at room temperature for a period of 24 hours and after that it was diluted by using ethyl acetate, and it was washed by using saturated sodium hydro carbonate aqueous solution, and saturated table salt aqueous solution. The organic layer was dried by using anhydrous sodium sulfate and it was concentrated under reduced pressure and the obtained by that crude synthesis material was again re-crystallized in ethyl acetate – hexane and 1.1 grams (yield of 80 %) of the target material (8), were obtained.

(8)

Rf = 0.49 (ethyl acetate: hexane = 1:1)

Mp: 88 ~ 89oC

$[\alpha]^{20}{}_{D}$ – 93.8° (C=0.93, CH3OH)

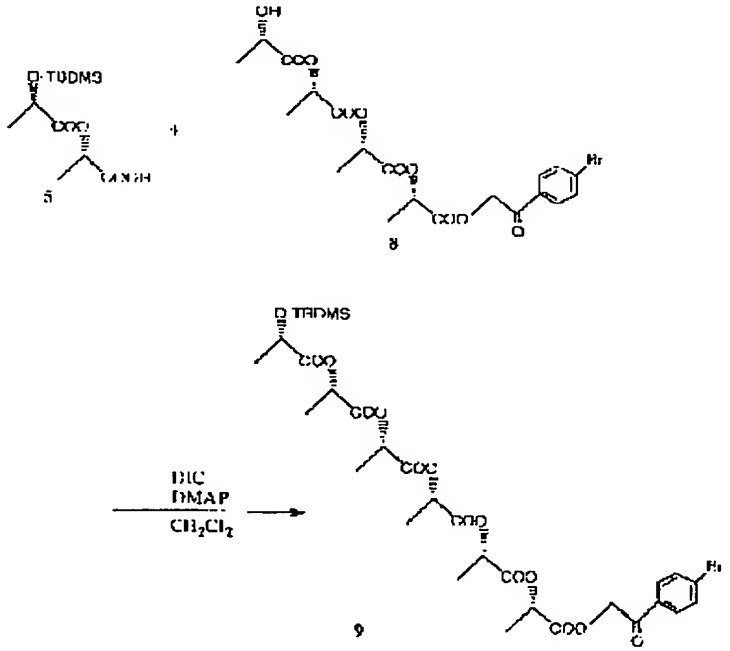
MS (FAB+, m-NBA) 503 [M (^{79}Br) + 1]$^{+}$ 431 [M (^{79}Br) – CH3OH (OH) CO]+, 361 [M (^{79}Br) – 2x CH3CH (OH) CO]+

^{1}H – NMR (270 MHz, CDCl3) δ: 7.625 ~ 7.619 ~ 7.779 (4H, m, aromatic protons: AA', BB'), 5.469 (1H, d, 16.5 Hz, AB type A part), 5.299 (1H, q, 7.0 Hz), 5.228 (1H, d, 16.5 Hz, AB type B part), 5.225 (1H, q, 7.3 Hz), 5.209 (1H, q, 7.3 Hz), 4.359 (1H, br, q, 7.0 Hz), 2.738 (1H, br, s, -OH), 1.667 (3H, d, 7.0 Hz), 1.610 (3H, d, 7.3 Hz), 1.600 (3H, d, 7.0 Hz)

[0043]

(Synthesis Example 8)

[Formula 12]



In a 100 ml flask, 1.63 grams (5.90 mmol) of the compound (5) obtained according to the Synthesis Example 4 were dissolved in 5.9 ml of methylene chloride, and the system was cooled to 0oC. To that, 485 mg (3.84 mmol) of diisopropyl carbo diimide were added,

and at a temperature of 0oC the material was stirred for a period of 10 minutes. Under a temperature of 0oC, 1.29 grams (2.65 mmol) of the compound (8) obtained according to the Synthesis Example 6 dissolved in 5.9 ml methylene chloride were added, and then after that 219 mg (1.79 mmol) of 4-dimethyl amino pyridine, were added. This was stirred for a period of 30 minutes at 0oC and after that it was concentrated under reduced pressure. This mixed material was suspended in ethyl acetate, and it was washed by using 10 % citric acid aqueous solution, saturated sodium hydro carbonate aqueous solution, and saturated table salt aqueous solution. The organic layer was dried by using anhydrous sodium sulfate and it was concentrated under reduced pressure. This mixed material was suspended in hexane, filtered, and the filtered solution where the sediment has been removed was obtained. The filtered solution was concentrated under reduced pressure and the obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 130 g., ethyl acetate: hexane = 2:8), and 1.80 grams (yield 92 % from compound (8)) of the target material (9), were obtained.

(9)

Rf = 0.39 (ethyl acetate: hexane = 1:3)

$[\alpha]^{20}{}_{D}$ – 104.4° (C=1.3, CH3OH)

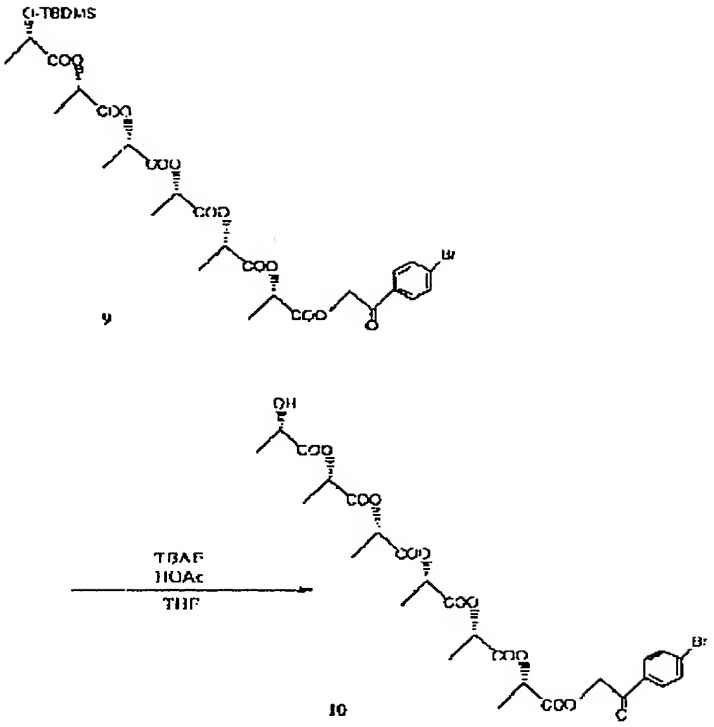
MS (FAB+, m-NBA) 761 $[M(^{79}Br) + 1]^+$ 783 $[(M(^{79}Br) + Na]^+$

^{1}H – NMR (270 MHz, CDCl3) δ: 7.626 ~ 7.778 (4H, m, aromatic protons: AA', BB'), 5.467 (1H, d, 16.2 Hz, AB type A part), 5.291 (1H, q, 7.0 Hz), 5.225 (1H, d, 16.2 Hz, AB type B part), 5.188 (1H, q, 7.3 Hz), 5.181 (1H, q, 6.8 Hz), 5.172 (1H, q, 6.8 Hz), 5.132 (1H, q, 7.3 Hz), 4.399 (1H, q, 7.0 Hz), 1.673 (3H, d, 7.0 Hz), 1.592 (3H, d, 7.3 Hz), 1.584 (6H, d, 6.8 Hz), 1.576 (3H, d, 7.3 Hz), 1.538 (3H, d, 7.0 Hz), 0.904 (9H, s, TBDMS), 0.110 (3H, s, TBDMS), 0.087 (3H,s, TBDMS)

[0044]

(Synthesis Example 9)

[Formula 13]



Inside a 50 ml flask, 1.30 grams (1.71 mmol) of the compound (9) obtained according to the above Synthesis Example 8, were dissolved in 3.4 ml of tetra hydro furan, under room temperature, and 1.17 ml (20.44 mmol) of acetic acid, 3.42 ml (3.42 mmol) of a 1 Mole concentration solution of tetra- n- butyl ammonium fluoride in tetrahydro furan, were sequentially added. This material was stirred at room temperature for a period of 24 hours, and it was then diluted by using ethyl acetate, and it was washed using saturated sodium hydro carbonate aqueous solution and saturated table salt aqueous solution. The organic layer was dried by using anhydrous sodium sulfate, and it was concentrated under reduced pressure and the obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 120 g., ethyl acetate: hexane = 1:1), and 1.00 grams (yield 92 %) of the target material (10), were obtained.

(10)

Rf = 0.49 (ethyl acetate: hexane = 1:1)

$[\alpha]^{20}{}_{D}$ – 116.1° (C=1.1, CH3OH)

MS (FAB+, m-NBA) 647 $[M\ (^{79}Br) + 1]^{+}$

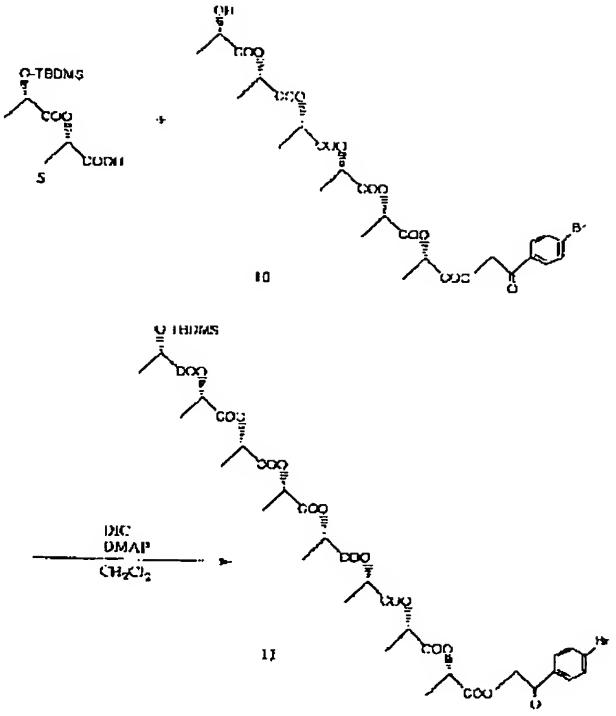
^{1}H – NMR (270 MHz, CDCl3) δ: 7.616 ~ 7.776 (4H, m, aromatic protons: AA', BB'), 5.464 (1H, d, 16.4 Hz, AB type A part), 5.291 (1H, q, 7.0Hz), 5.256 (1H, d, 16.5 Hz, AB type A part), 5.215 (1H, q, 7.3 Hz), 5.188 (2H, q, 7.0 Hz), 5.183 (1H, q, 7.0 Hz), 4.356

(1H, q, 7.0 Hz), 1.671 (3H, d, 7.0 Hz), 1.598 (9H, d, 7.0 Hz), 1.585 (3H, d, 7.3 Hz), 1.489 (3H, d, 7.0 Hz)

[0045]

(Synthesis Example 10)

[Formula 14]



In a 50 ml flask, 635 mg (2.30 mmol) of the compound (5) obtained according to the Synthesis Example 4 were dissolved in 2.3 ml of methylene chloride, and the system was cooled to 0oC. To that, 218 mg (1.73 mmol) of diisopropyl carbo diimide were added, and at a temperature of 0oC the material was stirred for a period of 10 minutes. Under a temperature of 0oC, 744 mg (1.17 mmol) of the compound (10) obtained according to the Synthesis Example 9 dissolved in 2.3 ml methylene chloride were added, and then after that 98 mg (0.80 mmol) of 4-dimethyl amino pyridine, were added. This was stirred for a period of 30 minutes at 0oC and after that it was concentrated under reduced pressure. This mixed material was suspended in ethyl acetate, and it was washed by using 10 % citric acid aqueous solution, saturated sodium hydro carbonate aqueous solution, and saturated table salt aqueous solution. The organic layer was dried by using anhydrous sodium sulfate and it was concentrated under reduced pressure. This mixed material was suspended in hexane, filtered, and the filtered solution where the sediment has been

removed was obtained. The filtered solution was concentrated under reduced pressure and the obtained crude synthesized material was purified by using silicagel column chromatography (Wako – gel C-300, 200 g., ethyl acetate: hexane = 2:8), and 819 mg (yield 77 % from compound (10)) of the target material (11), were obtained.

(11)

Rf = 0.28 (ethyl acetate: hexane = 1:3)

$[\alpha]^{20}{}_{D}$ – 121.1° (C=0.36, CH3OH)

MS (FAB+, m-NBA) 905 $[M (^{79}Br) + 1]^+$ 929 $[(M(^{79}Br) + Na]^+$

^1H – NMR (270 MHz, CDCl3) δ: 7.624 ~ 7.775 (4H, m, aromatic protons: AA', BB'), 5.461 (1H, d, 16.5 Hz, AB type A part), 5.288 (1H, q, 7.3 Hz), 5.228 (1H, d, 16.5 Hz, AB type B part), 5.131 (1H, q, 7.3 Hz), 5.128 ~ 5.228 (5H, m), 4.398 (1H, q, 7.0 Hz), 1.669 (3H, d, 7.0 Hz), 1.590 (3H, d, 7.0 Hz), 1.581 (12H, d, 7.3 Hz), 1.574 (3H, d, 7.0 Hz), 1.446 (3H, d, 7.0 Hz), 0.902 (9H, s, TBDMS), 0.109 (3H, s, TBDMS), 0.086 (3H,s, TBDMS)

[0046]

[Results From the Present Invention]

The L-lactic acid oligomer derivative materials according to the present invention are novel compounds and they do not contain similar materials with different various degrees of polymerization, and namely, they are pure compounds that have a constant length chain. These compounds are materials that are extremely effective as measuring materials for the living body activity detection relative to plants and animals, and also, they are extremely effective in the research fields of living body appropriate materials and drug delivery systems where the research has flourished in recent years.

Patent Assignee: Shimatsu Manufacturing Company

Translated by Albena Blagev

06/13/05